REMARKS

Claims 13, 15, 17, 18, 25, 26, 29, 30, 33-35, 43 and 47-69 are pending in the present application upon entry of this amendment. Claims 34, 35, 47, 49-53, 55-58, 61-62, 64 and 66-69 had been withdrawn from consideration as allegedly being drawn to a non-elected species. However, during the October 28, 2008 Examiner interview, the Examiner agreed that these claims should not have been withdrawn.

Claims 13, 17, 29, 30 and 59 have been amended. Specifically, claims 13, 29 and 59 have been amended to delete "an alkyl containing N" from the R_4 definition. Support for this amendment is found, *inter alia*, in compounds S7, S20, S27 and S36 in Appendix A. Claim 29 has further been amended and is now directed to a method of reducing the risk of sudden cardiac death, sustained VT and non-sustained VT in a subject by administering a compound of formula (g). Claims 17 and 30 have been amended to specify cardiac conditions selected from several conditions as listed in the claims. Claim 59 has further been amended and is now directed to a method of treating cardiac arrhythmia by administering a compound of formula (g). Support for these claim amendments is found, *inter alia*, in Figure 13 and in Example 14 on page 40 of the published application. No new matter has been added.

October 28, 2008 Interview

The applicants wish to thank the Examiner for the interview held on October 28, 2008 to discuss the outstanding rejections in the Office Action. The comments appearing herein are substantially the same as those that were presented and discussed during the interview. In particular, the applicants noted that claims 34, 35, 47, 49-53, 55-58, 61-62, 64 and 66-69, which have been withdrawn as allegedly being drawn to a non-elected species, encompass the compound S36, which had previously been elected by the applicants in a response dated November 1, 2007. The applicants further noted that, since the Examiner has found S36 to be free of the art and enabled, claims 34, 35, 47, 49-53, 55-58, 61-62, 64 and 66-69 should be reinstated and objected to as depending from a rejected independent claim, but should otherwise be indicated as allowable. The Examiner agreed and acknowledged that claims 34, 35, 47, 49-53, 55-58, 61-62, 64 and 66-69 would be reinstated in the application. In addition, the Examiner

acknowledged that the outstanding rejections under 35 U.S.C. §112 first paragraph, have been adequately addressed by the applicants during the interview.

Election

Claims 34, 35, 47, 49-53, 55-58, 61-62, 64 and 66-69 have been withdrawn from consideration. The applicants respectfully submit that this is an improper action. While it is permissible for the Examiner to examine a new species in the situation where the previously examined species is found to be free of art, it is not permissible to withdraw claims that were previously elected and directed to such species. MPEP 806.04 and 37 CFR 1.146 address this situation:

". . .the examiner may require the applicant in the reply to that action to elect a species of his or her invention to which his or her claim will be restricted if no claim to the genus is found to be allowable. However, if such application contains claims directed to more than a reasonable number of species, the examiner may require restriction of the claims to not more than a reasonable number of species before taking further action in the application."

The Examiner has acknowledged that the elected species, S36, is free of art and enabled, and for these reasons, should indicate that at least claims 34, 35, 47, 49-53, 55-58, 61-62, 64 and 66-69 are objected to as depending from a rejected claim, but are otherwise allowable. As noted above, during the interview, the Examiner agreed that claims 34, 35, 47, 49-53, 55-58, 61-62, 64 and 66-69 would be reinstated in the application. According to accepted PTO practice, the search must now be extended to a reasonable number of additional species. As further explained below, the additional compound that was searched by the Examiner has been distinguished by claim amendment, so that a further search of a reasonable number of additional species is required. The claims have been amended to recite a more defined sub-genus than the genus that was recited in the originally filed claims, and it is respectfully submitted that this sub-genus sets forth a reasonable number of species for examination.

Overview of Mechanism of Action

Before addressing the rejections raised in the office action, the applicants believe it would

be useful to provide an overview of ryanodine receptor biology in normal and disease states, and the mechanism of action by which the compounds of formula (g) are believed to exhibit their biological effects in reducing the risk of sudden cardiac death, sustained and non-sustained VTs.

The ryanodine receptor 2 (RyR2) channel comprises a large macromolecular signaling complex consisting of four RyR2 monomers, each binding one channel-stabilizing subunit FKBP12.6 (calstabin2). Phosphorylation of RyR2 by protein kinase A (PKA) is physiologically important since it plays a role in augmenting sarcoplasmic reticulum (SR) Ca^{+2} release during stress in order to increase cardiac output. PKA phosphorylation of RyR2 occurs as a downstream event in a signaling pathway that begins with the activation of β-adrenergic receptors via stimulation of the sympathetic nervous system, which activates adenylyl cyclase (AC) via specific G-proteins, resulting in the generation of cyclic AMP, which in turn activates PKA. This evolutionarily conserved mechanism is part of the "fight-or-flight" response that allows for rapid enhancement of cardiac contractility and cardiac output during exercise or stress.

PKA-phosphorylation of a serine residue (S2809) on RyR2 as a result of stress or exercise reduces the binding affinity of FKBP12.6 to RyR2, resulting in partial dissociation of FKBP12.6 from the macromolecular complex. The partial depletion of FKBP12.6 from the RyR2 complex increases the open probability (Po) of the channel resulting in increased intracellular Ca^{+2} release and augments the cardiac contractility under conditions of increased β-adrenergic signaling.

FKBP12.6 is also critical to normal RyR2 channel operation in the heart under resting conditions. Binding of FKBP12.6 stabilizes the RyR2 channel in the closed state during the resting phase of the cardiac contraction when the chambers fill with blood (diastole). Maintaining RyR2 in the closed state during diastole is critically important for preventing aberrant diastolic SR Ca^{+2} release (leak) that can trigger cardiac arrhythmias and sudden cardiac death.

Chronic stimulation of the sympathetic nervous system in heart failure (HF) and exercise which triggers fatal cardiac arrhythmias in individuals with Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) results in increased activity of PKA in cardiac muscle. PKA hyperphosphorylation of RyR2 results in depletion of FKBP12.6 from the RyR2 channel complex, resulting in "leaky" RyR2 channels, which have been demonstrated in HF patients and animal models of HF. Diastolic Ca^{2+} leak via RyR2 Po results in depletion of SR Ca^{+2} stores, contributing to reduced systolic RyR2 Ca^{+2} release. This Ca^{+2} leak during diastole can initiate

arrhythmias by activating a transient inward current (Iti), which causes membrane depolarizations resulting in delayed-after-polarizations (DADs) and triggered ventricular arrhythmias that can result in sudden cardiac death.

In CPVT patients, inherited RyR2 mutations reduce FKBP12.6 binding affinity for RyR2, resulting in the same type of diastolic Ca^{2+} leak via RyR2 as that which occurs in heart failure.. During exercise, PKA phosphorylation of RyR2 further depletes FKBP12.6 from the channel worsening the diastolic Ca^{2+} leak. PKA phosphorylation of phospholamban results in increased activity of the Ca^{2+} pump in the SR (SERCA2a) which increases the SR Ca^{2+} load further exacerbating the diastolic Ca^{2+} leak that activates DADs and triggers fatal ventricular arrhythmias and sudden cardiac death.

Compounds of formula (g) are calcium channel stabilizers ("rycals") that stabilize the interaction between FKBP12.6 and RyR2 by increasing the binding of FKBP12.6 to RyR2, even when the RyR2 is PKA hyerphosphorylated or has a CPVT mutation. By stabilizing the closed stated of the channel, rycals prevent diastolic SR Ca^{2+} leak and therefore prevent or reduce the risk of sudden cardiac death and ventricular arrhythmias.

Attached hereto as Exhibit A is an excerpt from a textbook entitled "Ryanodine Receptors, Structure, Function in Clinical Disease", edited by Dr. Andrew Marks, a named inventor on the present application, discussing the regulation of RyR by phsophorylation in the normal state, and during pathological conditions. Also attached as Exhibit B is a schematic representation of the mode of action of rycal compounds.

Rejections Under 35 U.S.C. § 112 First Paragraph

Claims 17, 29, 30, 33 and 43

Claims 17, 29, 30, 33 and 43 have been rejected under 35 U.S.C. § 112, first paragraph as allegedly not enabling a person skilled in the art to use the invention commensurate in scope with these claims. Applicants respectfully traverse the rejection.

The Office Action states at page 3 that the specification is "enabling for reducing the risk of sudden cardiac death, sustained VT and non-sustained VT with compound S36.", but that the specification "does not reasonably provide enablement for the treatment of cardiac conditions

generally or the broader class of compounds." Without conceding to the correctness of this rejection, and solely to advance prosecution, claim 29 has been amended and is now directed to a method of reducing the risk of sudden cardiac death, sustained VT and non-sustained VT by administering a compound of formula (g). The Examiner acknowledges that the specification is enabling for methods of reducing the risk of sudden cardiac death, sustained VT and non-sustained VT by administering the compound S36, therefore at least claim 35 is allowable.

The Examiner asserts, however, that the methods are not enabled for the full scope of the claims (i.e., the genus of formula (g)). The applicants respectfully disagree. First, by limiting the scope of formula (g) in the claims, the applicants have reduced the number of compounds encompassed in the methods of the present invention. The applicants submit that the methods of the present invention are fully enabled for the scope of formula (g), as amended. S36 is an illustrative member of formula (g). Applicants note that experimental data for one species can support patentability of an encompassing genus, especially when the data is presented for a representative member of the genus. This is particularly true in this case because a number of compounds of formula (g) have been shown to act on the same target as S36. Specifically, Figure 12 and Example 13 of the application as filed demonstrate that illustrative compounds of the claimed formula (g), S7, S20, S27 and S36, increase the binding of FKBP12.6 to RyR2 *in vitro*. Furthermore, applicants' submission in response to the previous office action (Attached hereto as Exhibit C) shows that compounds of claimed formula (g), including MolID Nos. 7, 27, 38, 58, 77, and 109, increase the binding of FKBP12.6 to RyR2. Thus, multiple illustrative compounds of the claimed formula (g) have been shown to work by the same mechanism as S36, i.e., by increasing FKBP12.6 binding to RyR2, similar to S36. In fact, the Examiner has acknowledged that methods of increasing the binding of FKBP12.6 to RyR2 that comprise administering compounds of the claimed formula (g) are enabled by the application as filed.

The applicants submit that compounds of formula (g), which act on the same target as S36, would reasonably be expected to be effective in methods of reducing the risk of sudden cardiac death, sustained VT and non-sustained VTs. As explained above, compounds of formula (g) are calcium channel stabilizers that stabilize the binding between FKBP12.6 and hyperphosphorylated RyR2 thereby stabilizing the closed stated of the channel and preventing diastolic SR Ca^{+2} leak. As further explained above, this mode of action results in the reduction

in the risk of sudden cardiac death and ventricular arrhythmias. Therefore, compounds which have been shown to stabilize the interaction of FKBP12.6 to RyR2, such as the compounds of formula (g), would be expected to be effective in methods of reducing the risk of sudden cardiac death, sustained VT and non-sustained VTs.

That stabilization of the binding of FKBP12.6 to RyR2 is reasonably expected to result in the reduction in the risk of sudden cardiac death and ventricular arrhythmias is further demonstrated by Lehnart et al., a peer reviewed article co-authored by Andrew Marks, one of the named inventors of the present application. A copy of Lehnart et al. (J. Clin. Invest. 118 (6), 2230-2245, 2008) is attached hereto as Exhibit D. Lehnart et al. demonstrate that leaky RyR2 channels in CPVT mice leads to cardiac arrhythmias, and that this can be prevented by treatment with S107, another rycal compound which stabilizes the binding between RyR2 and FKBP12.6 (see Abstract). In particular, Figure 4 on page 2236 shows representative telemetric ECG recordings from wild type mice and mice bearing a CPVT mutation, subjected to a stress protocol which results in sustained VTs (sVT) and sudden cardiac death. As shown in Figure (4)(D), S107 prevents stress-induced arrhythmias and sudden cardiac death in the CPVT mice. See also Figure 6, which shows using single channel measurements in lipid bilayers, that following stress, RyR2 channels from CPVT exhibit an increase in open probability of the channel (equivalent to leaky channels) and that this is reversed upon one week of S107 treatment. Figure 6 C-E demonstrate that RyR2 PKA phsophorylation is increased in response to stress resulting in FKBP12.6 depletion which can be prevented by pretreatment with S107. *This article thus demonstrates that a rycal which is structurally different from S36 stabilizes the interaction between RyR2 and FKBP12.6, and that this directly correlates with the prevention/reduction in ventricular arrhythmias and sudden cardiac death.* While S107 is not encompassed within the claimed genus, the article does demonstrate the direct link, that is accepted by those of ordinary skill in the art, between the ability of a rycal compound to stabilize the interaction between FKBP12.6 and RyR2, and its ability to reduce of VTs and sudden cardiac death.

Prior to this, Wehrens et al., another peer-reviewed article co-authored by Andrew Marks, a named inventor of the present application, demonstrated the link between FKBP12.6 deficiency and exercise-induced sudden cardiac death. See Wherens et al. Cell, 2003 113 pp. 829-840, a copy of which is attached hereto as Exhibit E. Wehrens et al. demonstrated that, during exercise,

RyR2 phosphorylation by cAMP-dependent PKA partially dissociates FKBP12.6 from the RyR2 channel, thereby increasing Ca^{+2} release and cardiac contractility, and that calstabin2 knockout mice exhibited exercise-induced cardiac VTs that caused SCD (see Summary on page 829 and Results on pages 830-835). This further demonstrates that FKBP12.6 deficiency destabilizes the RyR2 channel, leading to "leaky" Ry2 channels that can trigger fatal cardiac arrhythmias. The Wehrens paper also teaches that RyR2 from failing hearts exhibits the same defective (leaky) single channel properties as RyR2 from calstabin2 deficient mice and CPVT-associated RyR2 examined under exercise conditions (see, page 838, right column, second and third paragraphs).

Moreover, Wehrens et al., another peer-revised article co-authored by Andrew Marks, a named inventor of the present application, demonstrated that S2808A mice (where the RyR2 cannot be phosphorylated), are protected from heart failure. See, Wehrens et al., Proc. Natl. Acad. Sci., 2006, 103, pp. 511-518, Exhibit F.

Taken together, these papers (and others) demonstrate that FKBP12.6 depletion from RyR2 is associated with leaky RyR channels, and that leaky RyR2 channels are associated with cardiac dysfunction including heart failure, sudden cardiac death and ventricular arrhythmias. Compounds which are able to stabilize the interaction between FKBP12.6 and RyR2 prevent RyR2 leak and reduce the risk of ventricular arrhythmias and sudden cardiac death. Therefore, the applicants submit that claim 29 and claim 33 which depends therefrom are enabled so the rejection has been overcome and should be withdrawn.

Claim 17 depends from claim 13, and claims 30 and 43 depend from claim 29. Claims 17, 30 and 43 are not directed to treatment of subjects *per se*, but merely set forth the subject population or the specific conditions for the methods of claims 13 and 29. As such, claims 17, 30 and 43 are also enabled by the specification. In view of the amendments to claim 29, the applicants have amended claims 17 and 30 to specify the conditions which would be expected to have or are at risk of developing sustained and non-sustained VTs and sudden cardiac death. The applicants attach hereto as Exhibit G an except from a textbook entitled "Branuwald's Heart Disease, A Textbook of Cardiovascular Medicine, 8th Ed.", which demonstrates that the various conditions listed in claims 17 and 30 are associated with ventricular arrhythmias and sudden cardiac death. See, for example, Chapter 36, Table 36-2, and the Sections entitled "Dilated Cardiomyoathy and Heart Failure", "Acute Heart Failure", and Chapter 9, the Section entitled

"Caridac Events and Clinical Manifestations".

Thus, applicants believe that the rejection of claims 17, 29, 30, 33 and 43 under 35 U.S.C. § 112, first paragraph has been overcome, and respectfully request its withdrawal.

Claims 59, 63 and 65

Claims 59, 63 and 65 have been rejected under 35 U.S.C. § 112, first paragraph as allegedly not enabling a person skilled in the art to use the invention commensurate in scope with these claims. Applicants respectfully traverse the rejection.

Without conceding to the correctness of the rejection, and solely to advance prosecution, claim 59 has been amended and now recites "a method of treating cardiac arrhythmia." In addition, formula (g) has been reduced in scope as in claims 13 and 29, thereby limiting the number of compounds encompassed by the claimed genus. The Office Action states at page 3 that the specification is "enabling for reducing the risk of sudden cardiac death, sustained VT and non-sustained VT with compound S36." It is asserted that administering a compound of formula (g), of which S36 is a species, results in the reduction of risk of sustained VT and non-sustained VT and hence in the treatment of cardiac arrhythmia. The same arguments presented above for claim 29, are applicable to the rejection of claims 59, 63 and 65. Thus, applicants believe that the rejection of claims 59 and claims 63 and 65 which depend therefrom under 35 U.S.C. § 112, first paragraph has been overcome, and respectfully request its withdrawal.

Rejections Under 35 U.S.C. § 102

Claims 13, 15, 17, 18, 29, 30, 33, 43, 48, 54, 59, 60, 63 and 65 have been rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Kaneko et al. (US 5,416,066). The Office action states that Kaneko teaches a class of compounds allegedly encompassed by the instant claims, for treating and preventing myocardial infarction or cardiac death. In response, claims 13, 29 and 59 have been amended such that they do not encompass the compounds taught by Kaneko, since R_4 does not encompass an alkyl substituted by N. Thus, Kaneko does not anticipate claims 13, 19 or 59, or any of the claims dependent thereon. Accordingly applicants believe the rejection has been overcome and should be withdrawn.

In view of the above, applicants believe that the entire application is in condition for

allowance. Please contact the undersigned if any questions remain.

Please charge any deficiencies in the fees paid for this application, and credit any overpayments to Deposit Account No. 08-0219.

Respectfully submitted,

Date: November 6, 2008

/Jane M. Love, Ph.D./
Jane M. Love, Ph.D.
Reg. No. 42,812

Wilmer Cutler Pickering Hale and Dorr, LLP
399 Park Avenue
New York, New York 10022
Tel: (212) 937-7233
Fax: (212) 230-8888
jane.love@wilmerhale.com